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10/771,725	02/04/2004	Christophe Alain Thurieau	00537-178003	4960

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EXAMINER
TUCKER, ZACHARY C

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 01/13/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Offic Action Summary	Application N .	Applicant(s)	
	10/771,725	THURIEAU ET AL.	
	Examin r	Art Unit	
	Zachary C. Tucker	1624	

-- The MAILING DATE of this communicati n appears on the c ver sheet with the correspondence address --

Period f r Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-43* is/are pending in the application.

4a) Of the above claim(s) *2-8 and 10-43* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 9 and 11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9Sep04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Respons to Amendment

As requested in the correspondence filed 9 December 2004, which is in reply to the Requirement for Restriction mailed 14 September 2004, claim 9 has been amended.

Election/Restrictions

Applicant's election with traverse of the invention of Group I (claims 1-30) in the reply filed on 9 December 2004 is acknowledged. The traversal is on the ground that it is not possible for the examiner to search compounds without conducting the required search for pharmaceutical compositions and methods of treating diseases with the compounds. This is not found persuasive for the following reasons:

If a compound according to the invention is shown to be unpatentable, then it does not automatically follow that methods of treating certain diseases with that compound are unpatentable, or pharmaceutical compositions comprising that compound are unpatentable. The converse of this is true also – when a compound is patentable, the methods of using that compound to treat a disease are not necessarily patentable. Further searching is required to determine whether or not these additional embodiments are patentable if the compound is known. This search of the medical literature which is required in making the determination of whether or not a claimed method of treatment complies with the first paragraph of 35 U.S.C. 112 does not necessarily even include searching for compound of the invention; instead, that part of the search will often focus only on what is known about the relationship between the alleged biological activity of the claimed compounds and the disease states treated in the method claims. Method claims and pharmaceutical composition claims pose an

additional search burden above the search required for simple disclosures of a compound in the prior art.

Due to the nature of Markush practice, the search of the compounds will be stopped if art is found after the election of a species from the compound claims is made. Thus, a complete search of all disclosures of the claimed compounds, whether as part of a pharmaceutical composition, a simple report of a compound, or as a therapeutic agent in a method of treating a disease, is not conducted in cases where the search is stopped when art is found pursuant to an election of species.

If the search of all of the claimed compounds has not been completed, then the examiner is not in a position to make the determination of whether a pharmaceutical composition comprising one of the claimed compounds, or a method of treating a disease with one of the claimed compounds is patentable. To pretend that he could make that determination after not having searched completely the compound claims would be ill-advised to say the least.

Lastly, the inventions Grouped as I and II are patentably distinct, as demonstrated by the separate classification (class 514 *vs* 544, 546 or 548). Applicants argue that despite these different classifications, no serious search burden exists. According to the MPEP §803, "...a serious burden on the examiner may be *prima facie* shown if the examiner shows by appropriate explanation of separate classification, or separate status in the art, or a different field of search as defined in MPEP § 808.02. That *prima facie* showing may be rebutted by appropriate showings or evidence by the applicant." Applicant has made no rebuttal of the examiner's showing of separate

classification and separate status in the art. Thus, a serious burden has been established.

Applicants' election of the species of Compound 8, at page 200 of the instant specification is noted.

This species was searched, and no disclosure of the compound was found in the prior art whereupon the search was broadened to include all of claims 9 and 11 at which time art was found. Claims 2-8, 10 and 12-30 are withdrawn from consideration as not readable on the elected species, claim 11 has not been withdrawn from consideration because it was necessary to search all of claim 9, which claim 11 depends from. Claims 9 and 11 are the only claims that have been completely searched (see section headed "Allowable Subject Matter" *infra*).

Claims 31-43 are withdrawn from consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention.

The Restriction Requirement is still deemed proper and is therefore made FINAL.

Upon allowance of claim 1, method of use claims and pharmaceutical composition claims depending from claim 1 will be rejoined and examined for patentability, at which time the requirement for restriction between Group I and Group II will be withdrawn.

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re*

Ockert, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Instant claim 1 is provisionally rejected under 35 U.S.C. 101 as being an exact letter-for-letter duplicate of claim 1 in copending application serial no. 10/333,556.

All of the inventors in the instant case are listed as inventors in the copending application, but the copending application lists one additional inventor (Dennis Bigg, French citizen).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 9 and 11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for preparation of compounds of formula (I), the racemic-diasetereomeric mixtures, optical isomers and pharmaceutically acceptable salts thereof does not reasonably provide enablement for prodrugs of the compounds. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

As a guide to determining the scope of enablement provided by a given disclosure, the Office relies upon the following factors:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.
In re Wands, 858 F.2d 731,737 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)

(A) Though it might appear that the scope of instant claim 1 is limited to compounds of formula (I) having the structure depicted, it is not. A prodrug, as defined by Bundgaard in:

Hans Bundgaard, Design of Prodrugs, page 1. © 1985 Elsevier Science Publishers.

"is an inactive species, and therefore, once its job is completed, intact prodrug represents unavailable drug." Thus, an important requirement of prodrugs of compounds having the formula (I) is that they be pharmacologically inactive. Prodrugs come in myriad forms, and are not limited to only carboxylic esters, which are most commonly cited as examples, and suggested as the preferred type of prodrug on page 14 of the instant specification. A prodrug may be an amide, a Mannich base (imine), an acyclic precursor to a cyclic compound, a polymer-bound drug (either covalently or ionically), a compound of the drug covalently or ionically bound to another drug with different action or a carboxylic acid which is decarboxylated to provide the active drug.

So, the scope of all prodrugs is quite broad. A prodrug does not depend on the identity of the pharmacologically active agent formed from the prodrug for patentability. A prodrug is not necessarily structurally related to the compound of which it is a prodrug, since the metabolism *in vivo* of that compound is what provides the drug.

(B) Prodrugs of a compound having the formula (I) are the nature of the invention.

(C) The state of the prior art with respect to the development of prodrugs is represented by:

> Richard B. Silverman, The Organic Chemistry of Drug Design and Drug Action, pages 352-400. © 1992 Academic Press, Inc.
>
> Silverman teaches many kinds of prodrugs, including all of the types mentioned above in section "(A)." Pages 353 and 354 list eight various reasons why a prodrug would be desirable. On page 354, Silverman teaches that some prodrugs are discovered accidentally, and some designed on the basis of known metabolic transformations.

(D) The level of ordinary skill in the art is that of a medicinal chemist, holding a graduate level degree in the field and with experience in preparative organic chemistry.

(E) As discovery of prodrugs is sometimes accidental, then it follows that whether a given compound will function as a prodrug or not is sometimes unpredictable. On the other hand, when a compound is designed as a prodrug, one must first understand the metabolic milieu into which the presumptive prodrug is to be introduced, and must also know to what extent the compound will be metabolized. The metabolism of xenobiotics is not always predictable. A prodrug must also, by definition, be pharmacologically inactive, so one must know which modifications of the structure of the parent compound will render it inactive. Structure-activity relationships must in large part be determined empirically, although once a rule is discerned, the structure-activity of a given series of compounds becomes predictable.

Theoretically, if one of ordinary skill in the art knew all of the above variables, prodrug structure could be predicted in advance. The reality is that all of these considerations, in total, must be empirically devised when the compound in question is a novel compound, as is the compound having formula (I).

(F) No guidance nor any mention of prodrugs appears in the instant specification.

(G) No working examples of a prodrug appear in the instant specification.

(H) In order for one of ordinary skill in the art to practice the full scope of the prodrugs of compounds having the formula (I), a complete structure activity analysis would have to be completed. The practitioner would first screen for which type of modifications of the molecular structure would render an inactive compound. Then, the metabolic studies of all of the inactive compounds would have to be completed, and compounds that are converted to active compounds of formula (I) *in vivo* identified. This research would potentially be inconclusive and could take years. Additionally, one of ordinary skill in the art would necessarily have to undertake an effort to make totally new compounds not bearing any structural similarity to the compounds having the formula (I), such as the procyclic compounds converted to heterocyclic compounds *in vivo*, which are mentioned on page 360 of Silverman. Work with polymeric forms of the compounds having formula (I) would be necessary also. Because different animals' metabolisms differ to the extent that xenobiotics are handled by different enzymatic pathways, this effort would have to be duplicated in each species for which a prodrug were sought. As evidence that animals will differ substantially in the manner that xenobiotics are metabolized, the examiner presents:

Al-Dabbagh and Smith, "Species differences in oxidative drug metabolism: some basic considerations." Archives of toxicology. Supplement. Archiv fur Toxikologie. supplement, vol. 7, pages 219-231 (1984).

Al-Dabbagh and Smith states that the metabolic process itself is highly variable both between and within animal species, and that the toxic effect of many chemicals is a function of how the chemical is metabolized rather than the substance itself.

Given the amount of direction in the disclosure, this amount of experimentation is clearly undue. Applicants have not described the manner and process of making prodrugs of compounds having the formula (I), in such full, clear, concise, and exact terms as to enable any person skilled in the art to do so.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1,9 and 11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Deficiencies of claims 1, 9 and 11 under 35 U.S.C. 112, second paragraph are listed below:

In claim 1, recitation of "prodrugs thereof" is indefinite. Although one of ordianary skill understands what *function* a prodrug serves, he would not be able to identify all molecular structures which will be metabolized to a compound of formula (I) when subjected to some (unspecified) animals' metabolic process or processes. As stated above in the rejection of claims 1, 9 and 11 under the first paragraph of 35 U.S.C. 112, a prodrug of a compound need not be structurally related to the compound for which it

serves as a prodrug, because it is an animal's metabolism that provides the drug. So, a prodrug of a compound of formula (I) need not follow formula (I) at all. The exact metes and bounds of what group of chemical compounds are in fact prodrugs of a compound of formula (I) are not clear.

In the definitions of R^5 and Z^5 in claim 1, "C_0 alkyl" is recited (as part of a range). It is not understood what significance this has.

The proviso in claim 1 which reads as follows –

> "(c) when R^5 is H or (C_1-C_{12}) alkyl; R^6 is (C_1-C_6) alkyl; R^7 is (C_1-C_{12}) alkyl; and R^3 is –O-Z^{-2} or –S-Z^2, then Z^2 is not an optionally substituted moiety selected from the group consisting of phenyl, naphthyl, thiophene, benzothienyl and indolyl."

renders that claim indefinite because R^5 cannot be H.

Although the deficiencies under 35 U.S.C. 112, second paragraph arise only in claim 1, claims 9 and 11 are rejected under that statute as well because they depend from claim 1, which has been found to be indefinite.

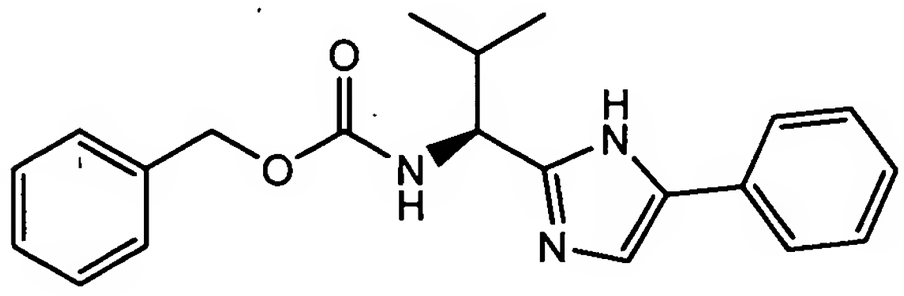
Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by th applicant for patent.

Claim 1 is rejected under 35 U.S.C. 102(a) and 102(e) as being anticipated by US 5,733,882 (Carr et al).

In column 27, at lines 28 and 29 of the Carr et al patent, preparation of the compound (1S)-1-carbobenzyloxyamino-1-isopropyl-1-(4-phenylimidazol-2-yl)methane as an intermediate for retroviral protease inhibitors is disclosed. The compound has this structural formula:



It is a compound according to claim 1 where R^1 and R^2 are H, R^3 is $-(CH_2)_m$-E-$(CH_2)_m$-Z^2, where both m are 0, E is a bond, and Z^2 is C_3 alkyl, R^4 is $-(CH_2)_m$-A^1. where m is 0, A^1 is $-C(=Y)$-X^2, where Y is O and X^2 is $-(CH_2)_m$-Y^1-X^3 where m is 0, Y^1 is O and X^3 is $-(CH_2)_m$phenyl, where m=1, R^5 is aryl and R^6 is H.

Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by FR 2.132.632 (Bornowski and Herzig).

Pages 6 and 7 disclose a compound according to instant claim 1. The compound designated B 417 in the table on page 7 of Bornowski and Herzig is a compound according to claim 1 where R^1 is H; R^2 is C_1 alkyl; R^3 is $-(CH_2)_m$-E-$(CH_2)_m$-Z^2 where both m are 0, E is a bond and Z^2 is H; R^4 is $-(CH_2)_m-A^1$ where m is 0 and A^1 is X^2 where X^2 is C_1 alkyl; R^5 is phenyl; R^6 is H.

Abstract of the Disclosure

The abstract of the disclosure is objected to because no depiction of the general structural formula of the compounds of the invention is provided, although reference to "imidazolyl derivatives of formula (I)" is made.

Correction is required. See MPEP § 608.01(b).

It is suggested that applicants include a general structure for the compounds of formula (I) in the abstract.

Information Disclosure Statement

The information Disclosure Statement filed 9 September 2004 has been considered by the examiner, but not in its entirety. Items denoted by letters D, P, Q, U, W, X, Y and Z were not present in the instant application's file, nor could those references be found in the parent application file (serial no. 09/719,457). If applicants kindly provide the references, the examiner will consider them.

Allowable Subject Matter

Claims 9 and 11 would be allowable if rewritten to overcome the rejections under 35 U.S.C. 112, first and second paragraphs, set forth in this Office action and to include all of the limitations of the base claim and any intervening claims.

Deletion of "prodrug," correction of the proviso in R^5 (which would be moot if R^3 in claim 1 is limited to the R^3's claim 9) and appropriate correction of the "C_0" alkyl recitations would overcome the rejections under 35 U.S.C 112.

Claims 9 and 11 are allowable over the prior art for the specific substitution pattern R^1=H, R^2=H, R^6=H, R^3= $-CH_2$-indol-3-yl, $-(CH_2)_4$-NH-CO-O-*t*-Bu, or $-(CH_2)_4$-NH_2

and R^5= phenyl, *o*-methoxyphenyl, *p*-Br-phenyl, *p*-nitrophenyl, or *p*-N,N-diethylaminophenyl.

The closest prior art with respect to instant claims 9 and 11 is:

von Geldern et al, "Azole Endothelin Antagonists. 1. A Receptor Model Explains an Unusual Structure-Activity Profile" Journal of Medicinal Chemistry, vol. 39(4), pages 957-967 (1996).

Compounds reported by von Geldern et al exhibit indol-3-yl-methyl at R^3, phenyl at R^5 and H at R^1 and R^2, but are substituted with –COOH at the position corresponding to R^6 in the instantly claimed compounds, which is not permitted. There is no suggestion given in von Geldern et al to replace this carboxylic group with H or alkyl.

Conclusion

Any inquiry concerning this communication should be directed to Zachary Tucker whose telephone number is (571) 272-0677. The examiner can normally be reached Tuesday-Thursday from 6:15am to 2:45pm, Monday from 6:15am to 1:45pm and Friday from 6:15am to 3:45pm (EST). If Attempts to reach the examiner are unsuccessful, the examiner's supervisor, Mukund Shah, can be reached at (571) 272-0674.

If, after a 24-hour period, Dr. Shah is unreachable, contact the examiner's acting supervisor, James O. Wilson, at (571) 272-0661.

The fax number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

zt

JAMES O. WILSON
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